

previous trials. A pooled analysis of data from individual patients will be informative for parsing out the effects of including versus not including glycoprotein IIb/IIIa inhibitors in the heparin control group; the use of heparin in the bivalirudin group; the effect of a postprocedural bivalirudin infusion (and different doses); outcomes with radial-artery versus femoral-artery access; treatment with clopidogrel versus more potent antiplatelet agents; and separate examination in patients with STEMI and those with non-STEMI,

given that the safety and effectiveness profile of bivalirudin may vary accordingly. No single study has been adequately powered to address all of these issues.

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Evaluation and Management of Lower-Extremity Ulcers

TO THE EDITOR: In their review article, Singer et al. (Oct. 19 issue)¹ mention the use of linezolid alone for the coverage of gram-positive and gram-negative and anaerobe bacteria in patients with diabetes who have lower-extremity infected ulcers. Linezolid is a synthetic oxazolidinone that inhibits the formation of the initiation complex for protein synthesis.² It has excellent skin and soft-tissue penetration,³ and in vitro studies suggest that linezolid may inhibit the bacterial toxin synthesis and modulate the host immune response.⁴ However, its antibacterial spectrum is mostly restricted to gram-positive aerobes and anaerobes, and it is much less active against gram-negative aerobes.² Severely infected lower-extremity ulcers in patients with diabetes are often polymicrobial, and gram-negative bacteria are commonly isolated, especially *Pseudomonas aeruginosa*.⁵

We question this antibiotic regimen when used as empirical therapy in patients in whom gram-negative organisms are commonly found. Our suggestion is to add an anti-gram-negative agent to linezolid, since the use of this antimicrobial agent alone could be inadequate.

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TO THE EDITOR: Lower-extremity ulcers are a tough health care problem and a terrible one for the patient. Singer and colleagues have tried to provide a comprehensive review on how these ulcers should be evaluated and managed. However, the importance of nutritional management of pressure ulcers was not adequately addressed. This is especially true in light of the strength of nutritional recommendations in recent guidelines.¹ In addition to high-calorie, high-protein nutritional support,¹ the provision of specific micronutrients that are involved in tissue regeneration results in improved healing. Those guidelines included a review of literature before the publication of a trial that not only confirmed the importance of nutritional support but also showed that such support has value beyond the treatment of malnutrition² as well as being cost-effective.³ Nutritional care should be an integral part of the multidisciplinary standards of care in patients with pressure ulcers.⁴

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TO THE EDITOR: In the differential diagnosis for lower-extremity ulcers, Singer et al. should have included calciphylaxis, which is a rare but frequently fatal vascular calcification disorder. It is characterized by painful skin lesions that typically involve the areas of cutaneous and subcutaneous adiposity that have rapid progression to ulcers with black eschar.¹ It occurs most commonly in patients with advanced chronic kidney disease, although the condition is also seen in patients with normal kidney function.² A high degree of clinical suspicion is usually needed for diagnosis.³ Accurate diagnosis is needed, since the treatment of calciphylaxis is different from the treatment of ulcers that have other causes. In addition to wound management, treatment may include discontinuation of certain medications (e.g., warfarin), the use of sodium thiosulfate, management of calcium and phosphorus levels,³ and possibly the administration of vitamin K.⁴

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THE AUTHORS REPLY: We thank Di Bella and colleagues for their comments on the choice of anti-

biotics in patients with diabetic foot infections and for giving us an opportunity to reiterate the importance of lower-extremity ulcers in individual patients and as a public health concern. Much needs to be learned regarding which organisms truly cause the spectrum of diabetic foot infections, since bacteria often colonize chronic wounds, swab cultures often do not represent the causative pathogenic organisms, newly developed molecular techniques have broadened our understanding of the wound microbiome, and not all prior studies have made a distinction between mild, moderate, and severe diabetic foot infections.^{1,2} Nonetheless, gram-positive organisms remain the most frequent types of organisms that are cultured. We agree that patients with chronic, extensive, or severe diabetic foot infections often have polymicrobial infections that require broad-spectrum antibiotics covering gram-positive cocci, obligate anaerobic organisms, and common gram-negative organisms (e.g., a fluoroquinolone plus clindamycin, piperacillin-tazobactam, and imipenem-cilastatin). Since many mild diabetic foot infections are usually caused by gram-positive cocci (especially when there has not been previous treatment with antibiotics), the Infectious Diseases Society of America (IDSA) recommends initial empirical therapy with a narrow-spectrum agent (e.g., cephalexin or dicloxacillin).³ Clindamycin, trimethoprim-sulfamethoxazole, or linezolid can be used if methicillin-resistant *Staphylococcus aureus* is highly suspected. A comprehensive discussion and list of potential antibiotics is provided in the 2012 IDSA clinical practice guidelines.³

We agree with Cereda that nutritional support is important, not only for patients with pressure ulcers but for all patients with hard-to-heal ulcers. Detailed data about evidence-based supplementation can be found in a Canadian Health Technology Assessment of interventions for pressure ulcers.⁴ However, much of the information linking malnutrition to pressure ulcers is derived from studies involving patients who have pressure ulcers that are not in the lower extremities. Finally, we thank Agarwal for the reminder that calciphylaxis may also be a rare cause of recalcitrant, nonhealing lower-extremity ulcers, and an index of suspicion is important in high-risk populations. We hope that our article and this correspondence will stimulate better research and patient care and result in improved out-

comes among patients with lower-extremity ulcers.

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Noninferiority Trials

TO THE EDITOR: Mauri and D'Agostino (Oct. 5 issue)¹ address the challenges in noninferiority trials. Yet an ethical issue was not discussed — how to convince candidate participants² that it is worth giving up part of the benefit provided by the current standard of care in exchange for advantages (e.g., convenience or fewer side effects) that are often of different clinical value than enhanced efficacy and are in any case not known at the outset of the trial.³ The authors illustrate their discussion using the case of noninferiority trials of new oral anticoagulants for the prevention of stroke and thromboembolism in patients with atrial fibrillation. Because the expected advantage of direct anticoagulants was the lower potential for hemorrhagic complications with those agents than with warfarin, the real trial question should have been how many fewer patients had major hemorrhage, stroke, or thromboembolism (an assessment of superiority) — not whether the proportion of patients who had stroke or thromboembolism was acceptably higher (an assessment of noninferiority). Do the authors think that trials really take into account the interests of the patients? If so, any noninferiority hypothesis can be translated into superiority.

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TO THE EDITOR: Mauri and D'Agostino view the choice of a noninferiority margin only on the basis of the effect of the active control over placebo. This approach is insufficient in the case of indications for which drug development is progressing rapidly and success rates of treatment are increasing (e.g., human immunodeficiency virus); in such cases, a noninferiority margin could be based on the difference between “best” and “second-best” active control.

The authors argue that to improve quality, noninferiority trials should provide “explicit justification of the acceptable margin”; however, in practice this is largely ignored.^{1,2} Do the authors believe that without such justification ethics committees should approve noninferiority trials?

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